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10/600,849	06/20/2003	Giovanni M. Pauletti	3715.12-1	8490
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		1616		
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/600,849

**Applicant(s)**

PAULETTI ET AL.

**Examiner**

Nathan W. Schlientz

**Art Unit**

1616

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 08 December 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 32-46 is/are pending in the application.
- 4a) Of the above claim(s) 43 and 44 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 32-42, 45 and 46 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB-08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Status of Claims***

Claims 32-46 are pending in the present application. Claims 43 and 44 are withdrawn as being drawn to a non-elected invention. As a result, claims 32-42, 45 and 46 are examined herein on the merits for patentability to the extent they read on the elected invention.

### ***Withdrawn Rejections***

Rejections and/or objections not reiterated from the previous Office Action are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 32-42, 45 and 46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application

was filed, had possession of the claimed invention. Claim 46 states that the method comprises pulsed drug delivery of an anti-migraine or anti-nausea drug into a systemic circulation. However, the instant specification only shows one specific example (Example 1) comprising sumatriptan, 15 wt.% distilled water, 67.5 wt.% SUPPOCIRE AS2X (saturated glycerides), 1.5 wt.% HPMC, and 15 wt.% TRANSCUTOL (ethoxydiglycol), which resulted in a pulsed release of active agent with the second peak occurring at about 300 minutes (Figure 1 and Table 1). In fact, Example 2 discloses a composition prepared using the identical procedure of Example 1 except sumatriptan was replaced with metoclopramide. This composition does not result in pulsed release when administered vaginally (Figures 2A and 2B, and Table 2). Therefore, Applicants have not described the invention in sufficient detail to convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Thus, for the purposes of search and examination, the examiner is construing the claims as if the term "pulsed drug" was omitted.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
  2. Ascertaining the differences between the prior art and the claims at issue.
  3. Resolving the level of ordinary skill in the pertinent art.
  4. Considering objective evidence present in the application indicating obviousness or nonobviousness.
1. Claims 32-42 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrison et al. (US 6,086,909) in view of Hagenlocher et al. (EP 0 391 852 A2) and Jannetta (US 2002/0055495).

***Determination of the scope and content of the prior art***

**(MPEP 2141.01)**

Harrison et al. teach a method for treatment of dysmenorrhea comprising an intravaginal drug delivery system containing an appropriate pharmaceutical agent incorporated into a pharmaceutically acceptable carrier whereby the pharmaceutical agent is released into the vagina and absorbed through the vaginal mucosa to provide relief of dysmenorrhea (abstract). Harrison et al. further teach the pharmaceutically acceptable carrier comprises a hydrophilic or hydrophobic carrier, such as semi-synthetic glycerides of saturated fatty acids with 8 to 18 carbons and PEG 6000/1500, respectively (column 8, lines 8-15). Also, Harrison et al. teach the pharmaceutical formulations further comprising a mucoadhesive agent, preferably hydroxypropyl methylcellulose (column 8, lines 16-22), and a penetration enhancer, preferably ethoxydiglycol (column 8, lines 23-28). Harrison et al. also teach the method of

applying the pharmaceutical formulation with the aid of an intravaginal delivery device, such as tampon device, vaginal ring, pessary, tablet, vaginal suppository, vaginal sponge, bioadhesive tablet, bioadhesive microparticle, cream, lotion, foam, ointment, solution and gel (column 2, lines 37-43; column 3, lines 8-67; column 4, lines 1-27; and column 9, line 4 through column 13, line 67). Harrison et al. also teach that preferred formulations for hydrophilic drugs comprise between about 60-90% by weight lipophilic carrier, between about 5-25% mucoadhesive agent, and between about 5-20% sorption promoter, whereas preferred formulations for lipophilic drugs comprise between about 50-90% by weight hydrophilic carrier, between about 5-20% mucoadhesive agent, and between about 5-25% sorption promoter (column 8, lines 31-34 and 44-47). Harrison et al. further teach that the drug delivery systems treat or prevent dysmenorrhea, and alleviate and prevent painful menstruation and symptoms such as nausea, fatigue, diarrhea, lower backache, and headache (col. 13, ll. 61-67).

***Ascertainment of the difference between the prior art and the claims***  
**(MPEP 2141.02)**

Harrison et al. teach that symptoms such as nausea as a result of dysmenorrhea are treated with their intravaginal drug delivery systems, but they do not teach using the instantly claimed anti-migraine or anti-nausea agents. However, Hagenlocher et al. teach that a plurality of medicines are suitable for rectal or vaginal therapy with the aim of making the medicines absorb systemically or in order to achieve an effect locally in the rectum or the vagina (pg. 2, ll. 3-6). Hagenlocher et al. teach a composition for rectal or vaginal application of drugs comprising at least one hydrocolloid, effective

substance(s), and possibly further carrier substances; wherein said compositions are used in systemic or local therapy for rectal or vaginal application (Abstract; pg. 2, ll. 44-46; and pg. 3, ll. 26). Hagenlocher et al. teach that effective substances include anti-emetic agents, such as metoclopramide, anti-epileptic agents, such as valproic acid, and neuroleptic agents, such as promethazine and chlorpromazine (pg. 3, ll. 30-49); the hydrocolloid includes hydroxypropylmethyl cellulose (pg. 4, ll. 22-37); and carrier substances include polyethylene glycol (pg. 4, ll. 43).

Also, Jannetta teaches suppositories for the treatment of nausea and vomiting, wherein the suppositories are optionally administered in the vagina and comprise metoclopramide ([0013]-[0018]). Jannetta also teaches that the metoclopramide is administered in a dosage of about 10 to about 20 mg twice or thrice a day ([0016]).

#### **Finding of *prima facie* obviousness**

##### **Rational and Motivation (MPEP 2142-43)**

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to incorporate anti-nausea drugs, such as metoclopramide and valproic acid, into the formulations of Harrison et al., because Hagenlocher et al. teach that vaginal therapy is an effective systemic treatment, and both Hagenlocher et al. and Jannetta teach that anti-nausea drugs can be administered as suppositories.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to

one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

### ***Response to Arguments***

Applicants argue on page 9 that no reference cited by the examiner or known to applicants teaches the delivery of anti-migraine or anti-nausea drug in a rapid pulsating manner resulting in at least 6 times faster drug release and extended presence of the drug in plasma. However, as discussed above, applicants have not shown that compositions other than the one disclosed in Example 1 result in a second pulse of drug release.

Applicants argue on page 11 that while the method [of the instant invention] seems to be similar to Harrison et al., it cannot be obvious from teaching of Harrison because the treated conditions are different, the sites of the treatment are different, the drugs to treat these conditions are different, the onset of the drug delivery is different and the amount of the drug in the plasma and its lasting effect is also different. However, the examiner respectfully argues that Hagenlocher et al. clearly teach vaginal administration of drugs wherein the medicines absorb systemically which leads to a relatively quick release, and in the case of systemic therapy to a quick absorption of the effective substances (pg. 2, ln. 1-6 and 29-32). Hagenlocher et al. even teach that preferred substances for systemic therapy include metoclopramide and valproic acid (pg. 3, ln. 30-31, 34, and 46-49; and claims 1, 5 and 7). Thus, Hagenlocher et al. clearly teach vaginal application of anti-emetic drugs, including metoclopramide and valproic acid, which results in systemic therapy. Also, Jannetta teaches vaginal

application of anti-emetic drugs, such as metoclopramide, which are suitable for treating acute or chronic diseases and infections that cause nausea, emesis, or associated symptoms (Abstract; [0013], [0014] and [0029]). Therefore, Jannetta clearly teaches systemic delivery of metoclopramide through vaginal application for the purpose of treating acute or chronic diseases and infections that cause nausea, emesis, or associated symptoms. Therefore, one of ordinary skill in the art would reasonably expect that using the vaginal delivery compositions according to Harrison et al. with metoclopramide or valproic acid as the active agent would lead to systemic delivery of the active. Also, it is well-known in the art that both valproic acid and metoclopramide are suitable for the treatment of migraines.

2. Claims 32-42, 45 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrison et al. (US 6,086,909) in view of Mahashabde et al. (US 2003/0133977) and Penkler et al. (US 6,255,502).

***Determination of the scope and content of the prior art***

**(MPEP 2141.01)**

The teachings of Harrison et al. are discussed above and incorporated herein by reference.

***Ascertainment of the difference between the prior art and the claims***

**(MPEP 2141.02)**

Harrison et al. teach that symptoms such as headache as a result of dysmenorrhea are treated with their intravaginal drug delivery systems, but they do not

teach using the instantly claimed anti-migraine or anti-nausea agents. However, Mahashabde et al. teach methods for treating migraine headaches through intravaginal delivery of selected serotonin reuptake inhibitors (SSRIs) to the systemic circulation (Abstract). Mahashabde et al. teach that the intravaginal delivery results in decreased side effects due to decreased serum concentration and/or reduced first pass metabolism ([0028]). Mahashabde et al. further teach that the intravaginal composition may be formulated with a variety of pharmaceutical carriers, such as polyethylene glycols, amenable for administration as creams, gels, foams, tablets, suppositories and pessaries ([0034]). Also, Penkler et al. teach that anti-migraine drugs, such as sumatriptan, naratriptan, almotriptan, zolmitriptan, rizatriptan and eletriptan (col. 7, ll. 45-48), are suitable for delivery to the vagina, such as in the form of a suppository (col. 13, ll. 1-30). Therefore, it was well-known at the time of the invention to treat migraine headaches systemically through intravaginal application of anti-migraine drugs.

#### **Finding of *prima facie* obviousness**

##### **Rational and Motivation (MPEP 2142-43)**

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to administer an anti-migraine drug, such as sumatriptan, naratriptan, almotriptan, zolmitriptan, rizatriptan and eletriptan, intravaginally in the formulation of Harrison et al. because it was well-known at the time of the invention to treat migraine headaches systemically through intravaginal application of anti-migraine drugs.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

### ***Response to Arguments***

Applicants argue on page 15 that no prior art made any disclosures regarding a rapid onset delivery of the anti-migraine or anti-emetic drug in pulsating manner, nor it shown any results that it would be able to achieve such results. However, as discussed above, applicants have not shown that compositions other than the one disclosed in Example 1 result in a second pulse of drug release.

The examiner notes that Mahashabde et al. clearly teach intravaginal delivery of active agents to the systemic circulation for the treatment of migraines (Abstract; and [0026], [0028], [0031], and [0034]), wherein because the actives pass through the mucosal wall of the vagina, the active agent directly enters the systemic circulation ([0027]). Thus, it would have been well within the purview of one of ordinary skill in the art to administer anti-migraine drugs to the vagina for systemic delivery.

### ***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

#### ***Contact Information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan W. Schlientz whose telephone number is (571)272-9924. The examiner can normally be reached on 9:00 AM to 5:30 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

NWS

/John Pak/  
Primary Examiner, Art Unit 1616